chiefly about the vasa vasorum of the aortic adventitia, with extension into the outer media.[5,26] Acute coronary arteritis, affecting the main branches of the coronary arteries, is even more common. DeBrito and colleagues found this in 14 of the 20 autopsies (70%) they performed for fatal leptospirosis.[5] Despite substantial inflammation, actual thrombosis of the coronary arteries was rare.[5] They also found that the presence of coronary arteritis closely correlated with histologic evidence of interstitial myocarditis.[5]

Valvular involvement may also occur in leptospirosis.[5] Two cases of vegetative endocarditis due to *Leptospira icterohaemorrhagiae* have been found at autopsy, but this is clearly an exceedingly rare phenomenon.[27]

Despite the clinical diagnosis of pericarditis in numerous patients with leptospirosis, autopsies usually fail to find significant pericardial inflammation. Whether an underlying epicarditis has been responsible for the pericardial friction rubs heard in these patients remains unknown.

Conclusion

A wide variety of cardiac manifestations may be seen in patients with severe leptospirosis. The mortality of these patients, who usually have both jaundice and azotemia, has been reported to range from 15% to 40%.[23,28] Despite myocardial involvement, death is usually the result of either renal or hepatic dysfunction.[28] Regardless of this, patients with severe leptospirosis should be closely observed for the development of cardiac involvement. Echocardiography or invasive hemodynamic monitoring may be useful tools in the management of either cardiomegaly or diffuse pulmonary infiltrates. With the prompt initiation of intravenous penicillin therapy, which is effective even when begun late in the course of the disease, it is hoped that the high mortality seen in these patients can be significantly reduced.[29]

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Adrenal Ganglioneuroma-Pheochromocytoma Secreting Vasoactive Intestinal Polypeptide

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THE RARE SYNDROME of watery diarrhea, hypokalemia, and achlorhydria (WDHA) is presumed to be due to hypersecretion of vasoactive intestinal polypeptide (VIP).[1] In adults, this syndrome is most commonly caused by hyperplasia, adenoma, or carcinoma of the pancreatic islet cells, but it may also occur in patients with bronchogenic carcinoma, medullary thyroid carcinoma, retroperitoneal histiocytoma, and pheochromocytoma.[2] In contrast, neurogenic tumors such as ganglioneuroma and neuroblastoma are its most common cause in children.[3]

In this report we describe the case of an adult with the WDHA syndrome who in addition had hypercalcemia, hypercalciuria, hypertension, and hyperglycemia. The lesion was located in the right adrenal gland by computed tomographic (CT) scan, and elevated catecholamine secretion was recorded. The cause was an adrenal ganglioneuroma-pheochromocytoma secreting VIP and catecholamines.

Report of a Case

The patient, a 61-year-old man, was referred for evaluation of renal calculi. When seen, however, his major symptoms were chronic watery diarrhea and episodes of flushing.

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ABBREVIATIONS USED IN TEXT

APUD = amine precursor uptake and decarboxylation [system]
CT = computed tomography
VIP = vasoactive intestinal polypeptide
WDHA = watery diarrhea, hypokalemia, and achlorhydria [syndrome]

The patient had had recurrent calcium nephrolithiasis, mild hypertension, hyperglycemia, and severe hypokalemia requiring more than 100 mEq per day of replacement therapy. Episodes of watery diarrhea began 3½ years before he was seen, but there had been no weight loss, nausea, vomiting, abdominal pain, tenesmus, mucus, or melena. This patient's diarrhea was resistant to several antidiarrheal agents but moderately responsive to fasting. In addition, the patient had sporadic episodes of facial and upper neck flushing. The only abnormality elicited on physical examination was a mildly elevated blood pressure of 142/90 mm of mercury with the patient standing.

Routine laboratory tests revealed normal values for liver function tests, complete blood count, sodium, chloride, bicarbonate, and urea nitrogen. The serum creatinine level was slightly elevated at 124 μmol per liter (1.4 mg per dl), and a random plasma glucose level was 9.9 mmol per liter (178 mg per dl). Serum potassium levels were maintained within the normal range only with the administration of 100 to 200 mEq of potassium chloride a day. Evaluation of the diarrhea revealed a 24-hour stool weight of greater than 2,000 grams, and stool fat measurements on two occasions were 53 and 190 mmol per day (15 and 54 grams per 24 hours; normal <18 mmol [5 grams] per day). Stool potassium levels were markedly elevated at 130 and 150 mmol per liter with simultaneous urinary potassium levels of 12 and 40 mmol per day. Radiologic studies including upper and lower gastrointestinal tract series were normal, as was a rectosigmoidoscopy. Gastrin, glucagon, and calcitonin levels were within normal limits. When the results of these studies suggested the WDHA syndrome, a VIP level was assayed and found to be elevated at 106 pmol per liter (320 pg per ml; normal 14 to 21.5 pmol per liter [42 to 65 pg per ml]).*

A workup for the cause of the renal calculi revealed a mild intermittent elevation of serum calcium levels, from 2.54 to 2.59 mmol per liter (10.2 to 10.4 mg per dl; normal 2.22 to 2.52 mmol per liter [8.9 to 10.1 mg per dl]), persistent hypercalciuria (urinary calcium 8.7 mmol [350 mg] per day) and mild hyperoxaluria (490 μmol [44 mg] per day). Parathyroid hormone concentrations were 44 and 71 μl equivalent per ml (normal <40 μl equivalent per ml). In addition, the patient had hypophosphatemia (0.39 to 0.90 mmol per liter [1.2 to 2.8 mg per dl]) and an elevated alkaline phosphatase level.

Because a pancreatic source of VIP hypersecretion was suspected, a CT scan of the abdomen was taken; it showed no abnormality of the pancreas, but a 5-cm right adrenal mass was identified. Further evaluation revealed that 24-hour values for urinary metanephrines and vanillylmandelic acid concentration were elevated at 9.3 μmol (1.7 mg) per day (normal <3.8 μmol [0.7 mg] per day) and 83 μmol (16.5 mg) per day (normal <50 μmol [10 mg] a day), respectively. In addition, a scintigraphic scan using iodine 131-labeled metaiodobenzylguanidine revealed increased isotope uptake in the right adrenal area.

Treatment with phenoxybenzamine hydrochloride, 20 mg twice a day, was started, and potassium chloride, 100 to 200 mEq per day, was continued. His blood pressure and serum potassium levels remained normal, but the diarrhea persisted. A month later, at abdominal exploration, a right adrenal tumor consistent with a pheochromocytoma was excised. During the operation a specimen of the right adrenal vein effluent was taken and found to have a VIP level of 264.8 pmol per liter (800 pg per ml). Extracts of the adrenal tumor tissue revealed a greatly elevated VIP concentration at 50 pg per mg of tissue.

The diarrhea ceased postoperatively, plasma VIP levels fell to 9.9 pmol per liter (30 pg per ml), and the patient's potassium level returned to normal without replacement therapy. A reevaluation of plasma catecholamine levels and urinary catecholamine metabolites showed normal values. Serum levels of parathyroid hormone, calcium, phosphorus, and magnesium were all normal after the adrenal tumor was resected.

Pathologic Description

The resected specimen was an adrenal gland measuring 3.5 by 2.5 by 2 cm with a cortical thickness of 0.2 cm that was attenuated at one end, at which point the medulla was contiguous with a tumor mass. The mass measured 5.9 by 5.5 by 4.5 cm and was encased in a bright yellow capsule. On sectioning, the tumor tissue was moderately firm with alternating areas of yellow and tan (Figure 1).

Histologically the tumor revealed two distinct patterns. Most areas sampled had a fibrous stroma with small and large nerve bundles. Embedded in the stroma were numerous large cells with granular cytoplasm and round nuclei containing prominent eosinophilic nucleoli resembling autonomic ganglion cells, a pattern consistent with ganglioneuroma (Figure 2, left). The rest of the tissue consisted of nests of smaller cells with varying amounts of cytoplasm, round to oval nuclei, and indistinct nucleoli, this being consistent with pheochromocytoma (Figure 2, right). Surrounding these

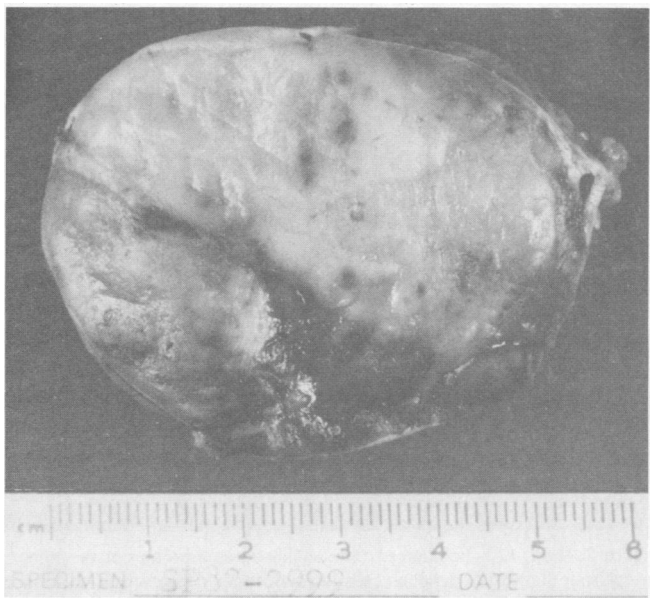

Figure 1.—The cut surface of adrenal tumor shows variegated yellow and red-brown areas.

*Plasma and tissue VIP assays were done by Sami I Said, MD, University of Illinois College of Medicine. Specificity data are from Said and Faloona.[1]

nests were interlacing capillaries. The two patterns merged with each other, although some distance from the border zones the patterns were distinct.

Special Studies

Unstained sections of the tumor were probed for the presence of VIP, calcitonin, and S-100 protein by the avidin-biotin-peroxidase complex technique.[4] Neither rabbit anti-calcitonin (Calbiochem) nor nonimmune rabbit serum showed staining (data not shown). Rabbit anti-S-100 serum (DAKO) strongly stained the Schwann cells in the ganglioneuroma element (Figure 3, left), as predicted from previous studies.[5] Rabbit anti-VIP serum (Calbiochem) strongly stained the cytoplasm of the ganglion cells, but there was only minimal cytoplasmic staining of the pheochromocytes (Figure 3, right).

Discussion

The production of peptide hormone is a property of cells derived from specialized ectoderm. The amine precursor uptake and decarboxylation (APUD) concept suggests that cells having the ability to produce peptide hormones are derived from a common neuroectodermal ancestry.[6] The APUD cells have two principal properties: they synthesize and store different types of amines, and they synthesize low-molecular-weight peptides.[7] Tumors arising directly from neural crest tissue offer a chance to explore ectopic hormone production.

In children, neurogenic tumors are common neoplasms of the posterior mediastinum and abdomen.[3] Ganglioneuromas have been reported in children in association with hypertension, diarrhea, or both. Because of the ability of neural crest tumors to secrete catecholamines, the pediatric literature previously ascribed an important role to these substances in the development of the diarrhea in patients with the watery diarrhea, hypokalemia, and achlorhydria syndrome.[8] With the availability of VIP assays and the elucidation of the properties of VIP, such as its role as a potent intestinal secretagogue, at least partially by the stimulation of adenylate cyclase, investigators suggested that this peptide's hypersecretion was involved in the cause of diarrhea.[9]

After Said and Mutt isolated VIP from porcine intes-

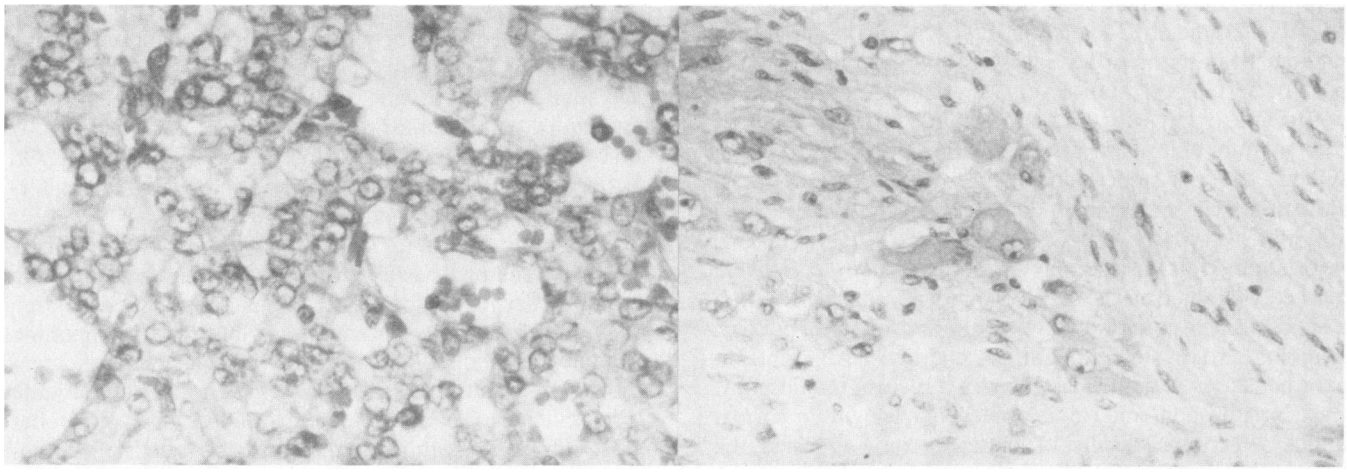

Figure 2.—Left, A micrograph of the ganglioneuroma portion of the tumor shows mature ganglion type cells, Schwann cells, and a fibrillary background (formaldehyde-fixed, paraffin-embedded tissue stained with hematoxylin-eosin [H&E]; original magnification x 400). **Right,** A micrograph of the pheochromocytoma portion shows typical cells in a "Zellballen" configuration with numerous capillaries (formaldehyde-fixed, paraffin-embedded tissue stained with H&E; original magnification x 400).

Figure 3.—Left, A micrograph of the ganglioneuroma portion of the tumor, after immunoperoxidase staining for vasoactive intestinal peptide, shows diffuse cytoplasmic staining of ganglion cells **(arrow)** (formaldehyde-fixed, paraffin-embedded tissue using avidin-biotin-peroxidase stain without counterstain; original magnification x 250). **Right,** A micrograph of the ganglioneuroma portion of the tumor, after immunoperoxidase staining for S-100 protein, shows nuclear staining of Schwann cells **(small arrow)** and staining of fibrils **(arrowhead)** (formaldehyde-fixed, paraffin-embedded tissue using avidin-biotin-peroxidase stain without counterstain; original magnification x 400).

tine,[10] high levels of this peptide were demonstrable in both serum and tumor tissue from children with the Verner-Morrison (or WDHA) syndrome. In these patients, the presence of mature forms of neural crest tumors and normal or increased catecholamine excretion was also documented.[11,12]

In adults, chronic watery diarrhea often complicated by hypokalemia and achlorhydria is frequently associated with pancreatic islet cell tumors.[13] Various nonpancreatic tumors, however, including pheochromocytoma, ganglioneuroblastoma, medullary thyroid carcinoma, and bronchogenic carcinoma have been described in association with the WDHA syndrome and elevated circulating plasma VIP levels.[1,2] The finding of two different histologic cell types in a single neoplasm of neuroectodermal origin was not described until Trump and co-workers reported the association of pheochromocytes and ganglion cells in an adrenal tumor of an adult with the WDHA syndrome.[14] Then in 1981 Choutet and associates reported finding both histologic types in an adrenal tumor incidentally found at laparotomy in a patient with hypertension and a family history of neurofibromatosis but no evidence of secretory diarrhea.[15] Recently a case has been reported of an adult patient with a pheochromocytoma-ganglioneuroma associated with the hypersecretion of VIP and secretory diarrhea.[16]

We describe the WDHA syndrome in a man with an adrenal ganglioneuroma-pheochromocytoma associated with high plasma and tumor tissue levels of VIP. Plasma VIP levels decreased with the concomitant cessation of diarrhea after surgical resection of the tumor. High vanillylmandelic acid and metanephrine levels were detected in this patient in association with mild hypertension. In previously described cases of WDHA found to be associated with pheochromocytomas, patients were not hypertensive.[14,16,17-21] This finding has been attributed to factors such as the dehydration resulting from severe diarrheal disease or the hypotensive effect of VIP. Unfortunately, in several of these patients catecholamine levels were not measured preoperatively. When elevated catecholamine levels have been recorded, the patients have been noted to have normal or low blood pressures. This case represents the first report of this disorder occurring in a hypertensive patient. After the resection of the adrenal tumor, vanillylmandelic acid and metanephrine excretion fell into the normal range; simultaneously, normal blood pressure levels were registered.

Intermittently high parathyroid hormone measurements and mildly elevated serum and urinary calcium levels were recorded during the course of the disease. After the operation, parathyroid hormone and serum calcium levels became normal, but urinary calcium excretion continued to fluctuate above the normal range. These mild elevations in serum and urinary calcium levels may have been related to the osteolytic activity of VIP,[9] although the persistence of urinary calcium variations after surgical therapy could have also been consistent with idiopathic hypercalciuria.

Normal gastrin, calcitonin, and glucagon levels were detected before the operation. These peptides and other substances including secretin, prostaglandins, pentagastrin, and gastrin inhibitory peptide have been postulated to be possible pathogenic factors leading to the clinical manifestations of pancreatic cholera.[12]

The findings in this case support the observation that tumors arising from neuroectodermal tissue have the ability to produce physiologically important peptides. The immunohistochemical studies done confirmed the production of VIP by ganglion cells. In contrast, the pheochromocytes did not stain for VIP. This finding agrees with the previous observations of Mendelsohn and colleagues who reported the presence of VIP in isolated ganglion cells of two pheochromocytomas whereas pheochromocytes and undifferentiated neuroblastic cells failed to stain for this peptide.[22] Nigawara and co-workers later reported similar findings.[21] Other investigators, however, have found VIP staining in both pheochromocytes and ganglionic cells.[20,23]

The detection of an elevated plasma VIP level may indicate the presence of neurogenic neoplasia. If catecholamine excretion is found to be elevated in a patient with the WDHA syndrome, the presence of an extrapancreatic tumor must be sought. Furthermore, its detection suggests that an underlying pheochromocytoma may be associated with other cells of neural crest origin responsible for the elevated circulating VIP levels.

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